Clinical considerations in selecting antiplatelet therapy in cerebrovascular disease

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Abstract: Effective antiplatelet drugs—aspirin, ticlopidine, dipyridamole, and clopidogrel—are reviewed.

Aspirin has remained the pharmacologic foundation of stroke prevention, primarily because of its low cost. It has been shown to provide a 22% relative risk reduction of stroke in high-risk patients. Its principal adverse effect is gastrotoxicity. Ticlopidine has been widely used in patients with a high risk of stroke who are sensitive to aspirin or in whom aspirin has failed. It has been associated with a median reduction in adenosine diphosphate-induced platelet aggregation of 70% in about 8–11 days. Ticlopidine has been shown to be superior to aspirin at three years in preventing stroke. The principal adverse effects are diarrhea and rash; there has been a 2.4% occurrence of neutropenia. In a trial comparing aspirin, dipyridamole, and a combination of the two, the risk of stroke was 18% lower with aspirin, 16% lower with dipyridamole, and 37% lower with combination therapy compared with placebo. The adverse-effect profile of dipyridamole has proven to be less problematic than that of aspirin or ticlopidine. In a trial comparing clopidogrel with aspirin, patients receiving clopidogrel had an annual 5.32% risk of ischemic stroke, myocardial infarction, or vascular death compared with 5.83% for patients receiving aspirin. Clopidogrel has been associated with a small occurrence of rash and diarrhea, and gastrointestinal intolerance and hemorrhage were less frequent with clopidogrel than with aspirin. Both aspirin and clopidogrel are associated with a low occurrence of neutropenia.

Aspirin, ticlopidine, dipyridamole, and clopidogrel have earned a role in stroke prevention; the different adverse-effect profiles of the drugs will influence the choice of agent.

Index terms: Aspirin; Cerebral ischemia; Cerebrovascular disorders; Dipyridamole; Drugs; Mechanism of action; Platelet aggregation inhibitors; Ticlopidine; Toxicity

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Stroke is the third leading cause of death in the United States and the leading cause of adult disability. An estimated 600,000 people suffer a new or recurrent stroke each year; 31% who have an initial stroke die within a year.[1] Those who survive become part of the nearly 4 million people disabled by stroke.

One in three stroke survivors needs assistance with such basic acts of daily living as dressing and eating.[1] One in five stroke survivors requires assistance to walk, and one in six ultimately requires institutional care because of the severity of his or her neurologic deficit.[1] Although stroke is generally a disease of the elderly, 35% of stroke survivors are between the ages of 35 and 65 and represent a major part of the work force.[1]

Despite the recent introduction of thrombolytic agents and the impact of these agents on stroke outcome, there is general agreement that prevention remains our most successful strategy. Antiplatelet agents are the key contribution of pharmacology to a successful stroke-prevention strategy. They help inhibit the aggregation of platelets and clot formation when atherosclerotic plaques rupture and release agonists. Antiplatelet agents can interrupt the evolution of thrombosis that might otherwise lead to embolization or vessel occlusion and ischemic stroke.

During the past 20 years a number of antiplatelet agents have been identified. All have been subjected to randomized, double-blind clinical trials to determine their individual and comparative value in stroke prevention. Some antiplatelet agents have proved efficacious, while others have been associated with troubling adverse events. Ideally, these trials would provide guidelines for the therapeutic use of those antiplatelet agents that have been shown to be beneficial. However, substantial differences in trial format, patient populations, study endpoints, and analyses make comparison of studies and agents difficult. The following discussion reviews the data available from these clinical trials to provide an overview of the effective antiplatelet drugs, including their risks and benefits.

Aspirin

In the late 1960s and early 1970s, aspirin was shown to inhibit irreversibly the platelet enzyme cyclooxygenase, thereby preventing the formation of thromboxane A_2 and blocking one major pathway of platelet aggregation.[2] Normal aggregation was shown to return in 7 to 10 days if aspirin was permanently discontinued.

Randomized clinical trials of aspirin for stroke prevention were begun during the 1970s. The Canadian

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Exhibit 18

Cooperative Trial used an aspirin dosage of 1300 mg daily in divided doses and showed a significant benefit of aspirin in preventing stroke compared with placebo.[3] However, many of the early trials, including the Canadian Cooperative Trial, appeared to provide conflicting or inconsistent results in subgroups of patients at high risk of stroke. The Canadian Cooperative Trial showed benefit for men but not women in prevention of stroke after transient ischemic attack, and it was not clear whether aspirin prevented recurrent stroke after an initial stroke. It was widely suspected that these inconsistencies were based on the small number of participants in most of the early trials.

The results of a meta-analysis of all antiplatelet trials up until 1990 have been published.[4,5] The meta-analysis was based on 145 randomized studies of antiplatelet therapy (primarily aspirin) in more than 70,000 patients considered at high risk of a "vascular endpoint" (defined as nonfatal myocardial infarction, nonfatal stroke, or vascular death). The Antiplatelet Trialists' Collaboration (ATC) demonstrated that antiplatelet therapy (primarily aspirin) for longer than one month significantly reduced the risk of a vascular event in men and women, not only after a transient ischemic attack but also after completed stroke. ATC found that the benefit provided was not influenced by age, hypertension, or diabetes. These results have been generalized to show that aspirin provides approximately a 22% relative risk reduction in patients at high risk of stroke.

The documented benefit of aspirin in preventing stroke must be balanced against the drug's established adverse-effect profile. Rare but severe allergy is a well-known adverse effect of aspirin, but the principal adverse effect is gastrotoxicity. This appears to increase with dose and results in gastric ulceration and potentially fatal gastrointestinal bleeding in approximately 1.5–2% of patients.[6] The risk of this alarming scenario continues throughout therapy and requires constant vigilance on the part of clinicians.

Despite its adverse-effect profile and modest performance in reducing the risk of stroke, aspirin has remained the pharmacologic foundation of stroke prevention, primarily on the basis of its low cost. Although 325 mg daily is the favored dosage, questions about a dose-dependent effect,[7] resistance,[8] and metabolism[8] in individual patients will continue to stir controversy over the "correct" aspirin dosage.

Ticlopidine

Ticlopidine, a thienopyridine derivative whose only pharmacologic activity is inhibition of platelet aggregation, was developed in France in the 1970s. Ticlopidine's mode of action is primarily inhibition of adenosine diphosphate (ADP)-mediated platelet activation. When given in the recommended dosage of 250 mg twice daily, ticlopidine has been associated with a median reduction in ADP-induced platelet aggregation of 70% in 8 to 11 days.[9,10]

Clinical trials of ticlopidine were carried out in North America in the 1980s. The Ticlopidine Aspirin Stroke Study (TASS)[11] and the Canadian American Ticlopidine Study (CATS)[12] were published in 1989. TASS compared ticlopidine 250 mg twice daily with aspirin 1300 mg daily in a randomized, double-blind trial of patients with recent transient ischemic attack, amaurosis fugax, resolving ischemic neurologic deficit, or minor stroke. Intention-to-treat analysis of the primary endpoint of nonfatal stroke or death from any cause showed ticlopidine to be superior to aspirin at three years, with a 12% lower risk ($p = 0.048$). Analysis of the secondary endpoint of myocardial infarction, stroke, or vascular death showed a 10% difference in relative risk at three years favoring ticlopidine. Although this result was not significant, it seems unlikely that the study had sufficient power to support this analysis. For the secondary endpoint of fatal or nonfatal stroke, the risk was 21% lower ($p = 0.024$) at three years with ticlopidine. CATS was a placebo-controlled, randomized, blind trial of ticlopidine 250 mg twice daily in patients with a recent moderate to major thromboembolic stroke. In an on-treatment efficacy analysis, ticlopidine was associated with a 30.2% lower frequency of myocardial infarction, stroke, or vascular death compared with placebo ($p = 0.006$). The occurrence of fatal and nonfatal stroke was 33.5% lower ($p = 0.008$). The risk difference in CATS was less robust when the data were analyzed by using an intention-to-treat strategy (23.3%, $p = 0.02$) in the outcome event of myocardial infarction, stroke, or vascular death.

The most frequent adverse events noted with ticlopidine were early diarrhea and rash. More disturbing was a 2.4% occurrence of neutropenia (<1200/mm^3). In 0.8% of patients the neutropenia was severe (<450/mm^3), resulting in permanent discontinuation of the drug. Neutropenia occurred during the first three months of therapy and was reversible in two weeks after termination of therapy. Rarely, thrombocytopenia may occur. Because of the possibility of neutropenia, blood counts are necessary every two weeks for the first three months of ticlopidine use.

Ticlopidine has been widely used in patients with a high risk of stroke who are sensitive to aspirin or in whom aspirin has failed. Aspirin failure has occurred most commonly in patients receiving aspirin for primary or secondary prevention of myocardial infarction who experience an initial transient ischemic attack. Wider use of ticlopidine has been slowed by concerns about neutropenia. Currently, ticlopidine is indicated for use only in patients who have had a stroke or transient ischemic attack and in patients who are intolerant of aspirin but who require treatment to prevent stroke.

Dipyridamole

The mechanism of action of dipyridamole is far less

clear than that of the other antiplatelet agents. Dipyridamole inhibits platelet aggregation by elevating cyclic adenosine monophosphate (cAMP) and inhibiting phosphodiesterase. This effect is reversible, and either frequent doses or a modified-release form of dipyridamole is required to maintain platelet inhibition.[2]

A number of clinical trials of dipyridamole alone and in combination with aspirin were carried out and published in the 1980s.[13-16] None appeared to show benefit of dipyridamole independent of the aspirin effect. These results limited the use of dipyridamole in stroke prevention in the 1980s and 1990s. The first European Stroke Prevention Study (ESPS I) showed that dipyridamole 75 mg and aspirin 325 mg taken three times daily were associated with a 33% lower primary endpoint of stroke or death from all causes at two years compared with placebo ($p < 0.001$).[17] This study was flawed by a 26% frequency of protocol violations and the absence of an aspirin-only treatment group. In ESPS II,[18] aspirin 50 mg daily, modified-release dipyridamole 400 mg daily, and a combination of the two were compared with placebo in 6602 patients in a blind, randomized trial. Data for the primary endpoints of stroke and stroke or death showed a significant effect for aspirin, dipyridamole, and the combination. The risk of stroke was 18% lower with aspirin ($p = 0.013$), 16% lower with dipyridamole ($p = 0.039$), and 37% lower with combined therapy ($p < 0.001$) compared with placebo. The risk of stroke or death was 13% lower with aspirin ($p = 0.016$), 15% lower with dipyridamole ($p = 0.015$), and 24% lower with combined therapy ($p < 0.001$) compared with placebo. The death rate alone was not affected by aspirin, dipyridamole, or the combination.

The adverse-effect profile of dipyridamole used alone consists primarily of dizziness, gastrointestinal distress, headache, and rash and has proved to be more benign than the adverse-effect profile of aspirin or ticlopidine.

The future role of dipyridamole alone or in combination with aspirin in stroke prevention is yet to be determined. However, causes for concern about ESPS II's study design include (1) the use of placebo when aspirin is already established as preventive therapy, (2) the use of low-dose aspirin when higher doses may be more beneficial, and (3) the rate of withdrawal due to dipyridamole, which indicates that additional studies are needed to define the role of dipyridamole in stroke prevention.

Clopidogrel

Clopidogrel is an ADP-receptor antagonist. It irreversibly inhibits binding of ADP to its platelet receptor and the subsequent activation of the glycoprotein IIb/IIIa complex. It is the (*S*) active enantiomer of a racemate differing otherwise from ticlopidine by the substitution of an acetate for a hydrogen at a single binding site. Clopidogrel was designed to avoid the undesirable bone marrow effects of ticlopidine.[19]

Clopidogrel has been studied in a single international clinical trial involving 19,185 patients.[19] Patients with atherosclerotic vascular disease manifested as recent ischemic stroke, myocardial infarction, or symptomatic peripheral arterial disease were assigned to treatment with either clopidogrel 75 mg daily or aspirin 325 mg daily in a randomized, double-blind trial. The primary endpoint was a composite outcome cluster of ischemic stroke, myocardial infarction, and vascular death. Mean follow-up was 1.91 years. On the basis of an intention-to-treat analysis, patients receiving clopidogrel had an annual 5.32% risk of ischemic stroke, myocardial infarction, or vascular death compared with 5.83% for patients receiving aspirin. This indicates a significant 8.7% difference in risk favoring clopidogrel ($p = 0.043$) over aspirin.[4] Analysis of individual subgroups initially suggested that the true benefit of clopidogrel might not be the same for each. A subsequent careful analysis of this apparent heterogeneity of effect suggested that it was due to play of chance and that the benefit of clopidogrel is likely to be the same for each subgroup.

The adverse-effect profile of clopidogrel has proved to be quite attractive. The neutropenia experienced with ticlopidine is absent with clopidogrel. A small occurrence of rash and diarrhea was noted. The frequency of gastrointestinal intolerance and hemorrhage was lower with clopidogrel than with aspirin, even when patients intolerant of or sensitive to aspirin were excluded from the trial. Clopidogrel will likely achieve an important role in preventing vascular events in patients with atherosclerotic vascular disease.

Future directions

Limitations of existing antiplatelet agents have led to the development of new strategies for better stroke prevention. Certainly further evaluation of different combinations of current drugs that work through different mechanisms (e.g., aspirin and clopidogrel) is likely. It is also possible that monoclonal antibodies against glycoprotein IIb/IIIa integrin shown to reduce clinical restenosis after coronary angioplasty may be beneficial in stroke prevention.[20] Finally, the role of warfarin in atherothrombotic stroke must be defined.

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